F

See US 3,168,526

PATENT SPECIFICATION

NO DRAWINGS

886,684

Date of Application and filing Complete Specification: Aug. 6, 1958.

No. 25220/58.

Application made in United States of America on Sept. 17, 1957.

Complete Specification Published: Jan. 10, 1962.

16

Index at acceptance:—Class 2(3), C1F2(C4: C5: D3), C1F3(C2: C4: D3), C2B3(A4: B: F: G1: G3: G8), C2B(30: 32), C3A13C(3C: 4C: 10H).

International Classification:—C07d.

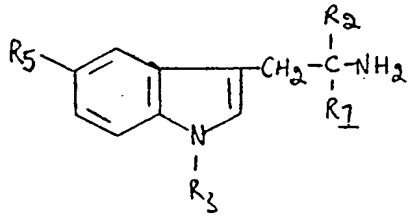
COMPLETE SPECIFICATION

Improvements in or relating to Heterocyclic Compounds and the manufacture thereof

We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

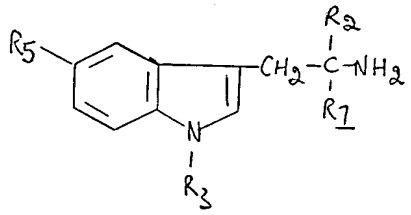
The present invention relates to a novel process for the preparation of 5 - hydroxy, 5 - benzyloxy and 5 - alkoxy - 3 - (2 - amino - 2 - alkylethyl) - indoles. This novel process is applicable to both 3 - (2 - amino - 2 - monoalkylethyl) - indoles and 3 - (2 - amino - 2,2-dialkylethyl) - indoles.

Such compounds are represented by the general formula:—



wherein R represents an alkyl radical containing from one to four carbon atoms inclusive e.g. methyl, ethyl, propyl or butyl, R_2 and R_3 represent hydrogen or an alkyl radical containing from one to four carbon atoms inclusive for example methyl, ethyl, propyl or butyl and R_5 represents hydroxy, a benzyloxy or benzhydryloxy radical optionally bearing alkyl, alkoxy or halogen substituents and containing up to 15 carbon atoms or an alkoxy radical containing up to 8 carbon atoms.

The invention is also concerned with novel indoles of the above class having the general formula:—



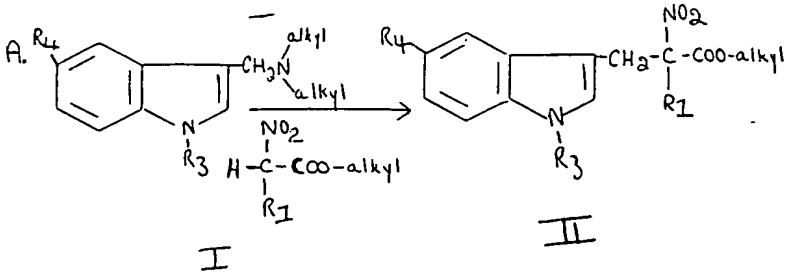
wherein R_1 represents an alkyl radical containing from one to four carbon atoms inclusive, R_2 and R_3 represent hydrogen or an alkyl radical containing from one to four carbon atoms and R_5 represents hydrogen, a benzyloxy or benzhydryloxy radical optionally bearing alkyl, alkoxy or halogen substituents and containing up to 15 carbon atoms or an alkoxy radical containing up to 8 carbon atoms provided that R_2 and R_3 do not represent hydrogen simultaneously and acid addition salts thereof which are prepared by the novel process.

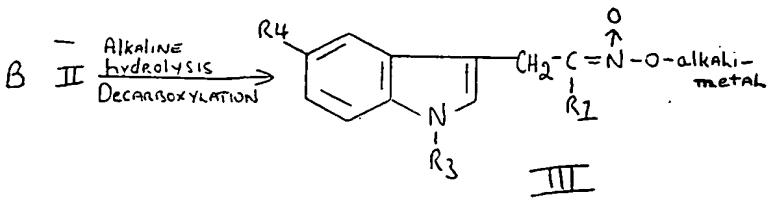
In the preparation of the hydroxy substituted compounds it is advantageous to prepare a benzyloxy or an alkoxy derivative and subsequently convert the benzyloxy or alkoxy radical to a hydroxy radical by various means which will be hereinafter recited. The alkoxy radical includes those radicals containing up to and including eight carbon atoms such as methoxy, ethoxy, isopropoxy, butoxy, octyloxy, and the like. The benzyloxy radical as stated above includes those radicals containing up to and including fifteen carbon atoms such as benzyloxy, benzhydryloxy, alkylbenzyloxy, e.g., paramethylbenzyloxy and para,para[1] - dimethylbenzhydryloxy, halobenzyloxy, e.g., para - chlorobenzyloxy and para,para[1] - dichlorobenzhydryloxy, alkoxybenzyloxy, e.g., para - methoxy - benzyloxy and para,para[1]-dimethoxybenzhydryloxy, and the like.

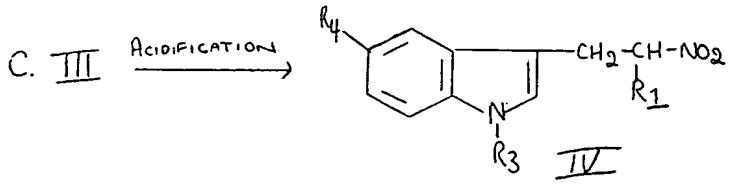
The 5 - hydroxy - 3 - (2 - amino - 2 - monoalkylethyl) - indoles and intermediates

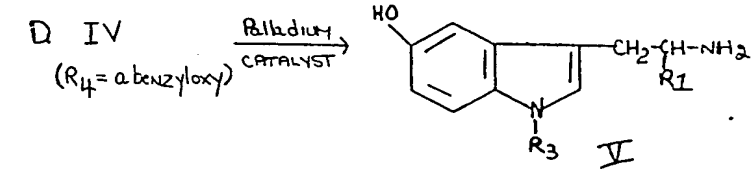
[*Price 4s. 6d.*]

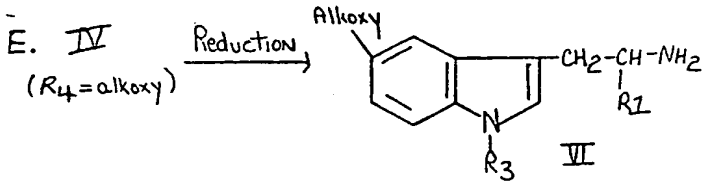
useful in the preparation of the same can be produced by the series of reactions shown below wherein R_1 and R_3 have the values given above. R_4 represents a benzyloxy or an alkoxy radical, which radicals can be converted to the hydroxy radical as noted above.

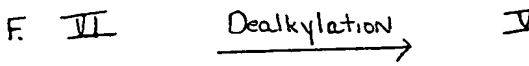


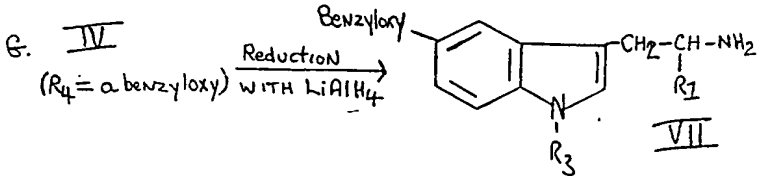


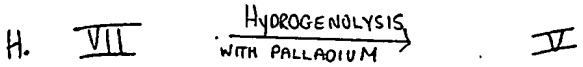












The process for the preparation of 5-hydroxy - 3 - (2 - amino - 2 - monoalkylethyl) - indoles (V) involves the following steps:

A. Nitroalkylating a 3 - (dialkylaminomethyl) - indole (I), e.g., 5 - benzyloxy - 3-(dimethylaminomethyl) - indole, with an alkyl ester of α - nitro - α - alkylacetic acid, such as ethyl α - nitro - α - methylacetate, ethyl α-nitro - α - isobutylacetate, methyl α - nitro - α - ethylacetate, propyl α - nitro - α - methylacetate, and the like, to produce an alkyl ester of α - alkyl - α - nitro - 3 - indolepropionic acid (II), e.g., ethyl 5 - benzyloxy - α - methyl-α - nitro - 3 - indolepropionate.

B. Hydrolysing and decarboxylating the alkyl ester (II) with an alkali such as sodium hydroxide, potassium hydroxide, and the like, to produce an alkli-metal salt of 3 - (2 - acinitro - 2 - monoalkylethyl) - indole (III), e.g., the sodium salt of 5 - benzyloxy - 3 -(2-acinitro - 2 - methylethyl) - indole.

C. Acidifying the alkali-metal salt (III) with an acid such as hydrochloric acid, acetic acid, nitric acid, phosphoric acid, and the like, to produce a 3 - (2 - nitro - 2 - monoalkylethyl)-indole (IV), e.g., 5 - benzyloxy - 3 - (2 - nitro - 2 - methylethyl) - indole.

The 3 - (2 - nitro - 2 - monoalkylethyl)-indole (IV) can be converted to a 5 - hydroxy-3 - (2 - amino - 2 - monoalkylethyl) - indole (V) in a variety of ways depending on whether R_4 is an alkoxy or a benzyloxy substitutent.

D. When R_4 is a benzyloxy radical the concomitant conversion can be accomplished by hydrogenolysis and hydrogenation in the presence of a palladium catalyst such as palladium black, palladium - barium sulphate, palladium charcoal, and the like.

E and F. When R_4 is an alkoxy radical the conversion can take place in two steps, e.g., (1) reduction of the nitro group with lithium aluminum hydride or with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum oxide, or palladium, as disclosed in U.S. patent 2,557,041, and (2) dealkylation with aluminum chloride utilizing the procedure of Asero et al. (Ann. 576, 69, 1952).

G. and H. When R_4 is a benzyloxy radical

the conversion can also be accomplished in two steps such as (1) reduction of the nitro group with lithium aluminum hydride, and (2) hydrogenolysis of the benzyloxy radical in the presence of a palladium catalyst.

In the above process 5 - alkoxy - 3 - (2-amino - 2 - monoalkyl - ethyl) indoles (VI) and 5 - benzyloxy - 3 - (2 - amino - 2 - monoalkylethyl) - indoles (VII) can be advantageously isolated as acid addition salts by reacting the free basee with a stoichiometric quantity of an acid, such as hydrochloric, picric, hydrobromic, sulphuric, acetic, tartaric, citric, or the like. The 5 - hydroxy - 3 - (2 - amino - 2 - monoalkylethyl) - indoles (V) can also be converted to acid addition salts, if so desired. For example, a solution of the desired acid addition salt can be prepared by mixing stoichiometric amounts of a free base of the invention with an organic or inorganic acid in the presence of water. Examples of acids are hydrochloric, oxalic, picric, hydrobromic, tartaric, citric, acetic, sulphuric, as well as a mixture of sulphuric acid and a stoichiometric quantity of creatinine sulphate. The preferred acids are oxalic, picric, tartaric, citric, acetic, as well as the mixture of sulphuric acid and creatinine sulphate.

The novel 5 - hydroxy - 3 - (2 - amino-2,2 - dialkylethyl) - indoles can be prepared by nitroalkylating a 3 - (dialkyl - aminomethyl) - indole (I) with a nitroalkane instead of utilizing an alkyl ester of α - nitro - α - alkylacetic acid as shown in the process outlined above. The process which can be employed is disclosed by Snyder et al., J. Am. Chem. Soc. 69, 3140, 1947. The nitroalkanes which can be employed include those compounds wherein the nitro radical is attached to a carbon atom containing one active hydrogen. Nitroalkanes which can be used include, e.g., 2 - nitropropane, 2 - nitrobutane, 3-nitropentane, 2 - methyl - 3 - nitroheptane, and the like. The nitroalkylation results in the preparation of 3 - (2 - nitro - 2,2 - dialkylethyl) - indoles which can be converted to 3 - (2 - amino - 2,2 - dialkylethyl) - indoles in the same manner as the above-identified 3 - (2 - nitro - 2 - monoalkylethyl) - indoles (IV) are converted to 3 - (2 - amino - 2 - monoalkylethyl) - indoles (V). The 3 - (2-amino - 2,2 - dialkylethyl) - indoles (V). The 3 - (2 - amino - 2,2 - dialkylethyl) - indoles can also be converted to acid addition salts, if so desired, in the same manner as the 3-(2 - amino - 2 - monoalkylethyl) - indoles, noted above.

The starting 3 - (dialkylaminomethyl)-indoles (I) can be prepared by reacting a suitably substituted indole with a dialkylamine in the presence of formaldehyde. For example, the procedures disclosed by Ek et al., (J. Am. Chem. Soc. 76, 5579, 1954), Rydon et al., (J. Chem. Soc. 2462, 1951), and Bell et al., (J. Org. Chem. 13, 547, 1948), who show the preparation of 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole, 5 - ethoxy - 3 - (dimethylaminomethyl) - indole, and 5 - methoxy-3 - (dimethylaminomethyl) - indole, respectively, can be employed.

The starting indoles suitably substituted in the 1 or 5 - position can be prepared according the following procedures:

(1). The 5 - benzyloxyindoles are prepared in the manner disclosed by Burton et al., J. Chem. Soc. 1726, 1937.

(2). The 5 - alkoxyindoles are prepared by the procedure outlined by Blaikie et al., (J. Chem. Soc. 296, 1924) for the preparation of 5 - methoxyindole by utilizing the requisite alkoxy - 2 - nitrotoluene.

The 1 - alkyl - 5 - substituted indoles can be prepared by the process described by Baker, J. Chem. Soc. 458, 1940, or Potts et. al., J. Chem. Soc. 2641, 1954, wherein the 1-alkyl substituent is added by reacting a 1 - unsubstituted indole with an alkyl halide in the presence of an alkali-metal alkoxide or amide.

Representative indoles which can be employed to produce 3 - (dialkylaminoethyl)-indoles include the following: 5 - benzyloxyindole, 5 - ethoxyindole, 5 - (paramethylbenzyloxy) - indole, 5 - benzhydryloxyindole, 5 - (para,para[1] - dimethylbenzhydryloxy)-indole, 5 - (para - ethoxybenzyloxy) - indole, 5 - methoxyindole, 5 - propoxyindole, 5 - isopropoxy - indole, 5 - butoxyindole, 1 - methyl-5 - benzyloxyindole, 1 - ethyl - 5 - ethoxyindole, 1 - propyl - 5 - propoxyindole, 1 - propyl - 5 - (para - propylbenzyloxy) - indole, 1 - methyl - 5 - (parachlorobenzyloxy) - indole, 1 - methyl - 5 - methoxyindole, and the like.

The alkyl esters of α - nitro - α - alkylacetic acid utilized in the preparation of the alkyl esters of α - alkyl - α - nitro - 3 - indolepropionic acid (II) can be produced utilizing the procedure of Kornblaum et al., J. Am. Chem. Soc. 77, 6654, 1955, who show the preparation of ethyl α - nitropropionate and ethyl α - nitrobutyrate.

The 5 - hydroxy - 3 - (2 - amino - 2 - monoalkylethyl) - indoles and 5 - hydroxy-3 - (2 - amino - 2,2 - dialkylethyl) - indoles of the present invention have shown valuable oxytocic activity. The 5 - hydroxy - 3 - (2-amino - 2 - monoalkylethyl) - indoles and 5-hydroxy - 3 - (2 - amino - 2,2 - dialkylethyl)-indoles of the present invention have also demonstrated the ability to resist oxidative deamination by the enzyme, monamine oxidase, to an excellent degree. These compounds have not only demonstrated this valuable property of being able to resist oxidative deamination but, moreover, they are also able to inhibit the enzymatic destruction of other amines which are normally affected by the enzyme. For example, serotonin [5 - hydroxy - (3 - (2 - aminoethyl) - indole creatinine sulphate] is materially affected by monamine oxidase. The ready deamination of serotonin by the

enzyme has been reported by Govier et al., Science 118, 596, 1953 and Blaschko et al., J. Physiol. 122, 403, 1953. It is obvious that if adequate levels of serotonin in the body are to be maintained then the enzymatic activity must be eliminated or reduced. For example, the desirability of proper serotonin-level maintenance in the brain has been reported by Woolley, Science 125, 752 (1957). The 5-hydroxy - 3 - (2 - amino - 2 - monoalkylethyl)-indoles and 5 - hydroxy - 3 - (2 - amino - 2,2 1 dialkylethyl) - indoles of the present invention are able to provide this highly desirable protective property. Table I shows the results obtained when varying concentrations of 5 - hydroxy - 3 - (2 - amino - 2 - methylethyl) - indole (I) or 5 - hydroxy - 3-(2 - amino - 2,2 - dimethylethyl) - indole (II) are combined with serotonin and the mixture subjected to monamine oxidase activity. The monamine oxidase activity was measured by the manometric procedure of Bhagvat et al., Biochem. J., 33, 1338, 1939. The source of enzyme was the guinea pig liver and the oxygen consumption of the liver alone, nineteen cubic millimeters is substracted in every case. The concentration of serotonin in each example is 0.0063 mole.

TABLE I

	Molar Concentration	mm^3 O_2 consumed in 50 minutes	Percent Inhibition
Serotonin	0.0063	159	
Inhibitor			
I	0.0124	52	76
	0.0041	94	47
	0.0013	123	26
	0.0004	140	14
II	0.04	66	66
	0.02	92	48
	0.01	114	32
	0.006	135	17
	0.003	144	11

Thus it is seen that when serotonin is combined with varying concentrations of 5-hydroxy-3 - (2 - amino - 2 - methyl - ethyl) - indole or 5 - hydroxy - 3 - (2 - amino - 2,2 - dimethylethyl) - indole oxygen consumption is reduced, which is a clear indication that monamine oxidase destruction of the pharmacologically active serotonin has been inhibited.

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

EXAMPLE 1

Preparation of 5 - hydroxy - 3 - (2 - amino-2 - methylethyl) - indole creatinine sulphate

A. *5 - benzyloxy - 3 - (dimethylaminomethyl) - indole*

Fifty milliliters of dioxane and fifty milliliters of glacial acetic acid were placed in a one-liter, three-necked flask equipped with a stirrer, condenser, and addition funnel. The solution was cooled in an icebath and four milliliters of thirty percent aqueous formaldehyde solution was added with stirring, followed by eleven milliliters of 25 percent aqueous dimethylamine solution. 5-Benzyloxyindole (11.15 grams) was dissolved in fifty milliliters of dioxane and added dropwise to the reaction mixture. The cooled solution was then stirred for two hours. The ice-bath was then removed and stirring was continued at about 25 degrees centigrade for about ten hours.

Water (625 milliliters was added to the reaction mixture along with five grams of diatomaceous earth and five grams of decolorizing carbon. The mixture was filtered through five grams of diatomaceous earth on a course sintered funnel. The resulting slightly

cloudy solution was cooled with ice. A cold solution of forty grams of sodium hydroxide in 500 milliliters of water was added. The mixture was kept in ice for about one hour, was filtered, and the precipitate was washed with water.

The precipitate, 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole, was dried at 25 degrees centigrade. The yield was 13.1 grams (93.5 percent) and the compound melted at 134 to 139 degrees centigrade.

B. *Ethyl 5 - benzyloxy - α - methyl - α - nitro - 3 - indole - propionate*

A mixture of 9.76 grams of 5 - benzyloxy-3 - (dimethyl - aminomethyl) - indole, 5.13 grams of ethyl α - nitro - α - methyl - acetate (Kornblum et al., J. Am. Chem. Soc. 77, 6654, 1955), and 58 milliliters of anhydrous toluene was stirred and refluxed for three and one-half hours while passing a rapid stream of nitrogen through the mixture. The mixture was cooled to 25 degreese centigrade and 100 milliliters of chloroform was added. The cooled mixture was successively washed with two thirty-milliliter portions of ten percent hydrochloric acid, once with thirty milliliters of water, twice with thirty milliliters of five percent aqueous potassium hydroxide solution, once with thirty milliliters of water, and once with saturated aqueous sodium chloride solution. The mixture was then dried over anhydrous sodium sulphate and evaporated to drynes to yield 12.8 grams (97 percent), of ethyl 5 - benzyloxy - α - methyl - α - nitro-3 - indolepropionate as a brown oil.

C. *Sodium salt of 5 - benzyloxy - 3 - (2-acinitro - 2 - methylethyl) - indole*

A solution of 3.6 grams of sodium hydroxide in ten milliliters of water was added to a solution of 12.8 grams of ethyl 5 - benzyloxy-α - methyl - α - nitro - 3 - indolepropionate in 53 milliliters of absolute ethanol. The mixture was allowed to stand at 25 degrees centigrade for 24 hours. The resulting suspension was then diluted with ten milliliters of absolute ethanol, filtered, and the precipitate was washed with two ten-milliliter portions of ethanol and then with a total of forty milliliters of ether. The reulting solid, the sodium salt of 5 - benzyloxy - 3 - (2 - acinitro - 2 - methylethyl) - indole, weighed 12.28 grams. A. 1.5 gram sample of the sodium salt was further purified by slurrying the crude salt in ten milliliters of water, filtering the resulting suspension, and washing the precipitate slowly with three milliliters of water. The slightly wet solid was mixed with acetone and heated on a steam bath. Warm water was added to the mixture until the solution cleared, followed by addition of warm acetone until precipitation occurred. The mixture was cooled in an ice bath and filtered. The purified sodium salt precipitate weighed 1.1 grams and melted at 112 to 115 degrees centigrade.

Anal.: Calcd. for $C_{18}H_{17}N_2O_3Na$: Na, 6.92
Found: Na, 6.51.

D. *5 - benzyloxy - 3 - (2 - nitro - 2 - methylethyl) - indole*

The sodium salt of 5 - benzyloxy - 3 - (2-acinitro - 2 - methylethyl) - indole (approximately 12.18 grams) was dissolved in one liter of water by warming to forty degrees centigrade. The solution was cooled to about seven degrees centigrade and acidified with 25 milliliters of ten percent hydrochloric acid while cooling. The resulting precipitate was filtered and washed with 100 milliliters of water, and the precipitate was dried by suction and allowed to stand at 25 degrees centigrade for 56 hours. The resulting product was dissolved in 150 milliliters of ether. The ether solution was dried over anhydrous magnesium sulphate and concentrated to produce 7.5 grams of 5-benzyloxy - 3 - (2 - nitro - 2 - methylethyl)-indole as an oil which later crystallized. This compound, after two recrystallizations from ether-petroleum ether mixture, melted at 83 to 85 degrees centigrade.

Anal.: Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03
Found: C, 70.15; H, 6.11; N, 9.27.

E. *5 - benzyloxy - 3 - (2 - amino - 2-methylethyl) - indole hydrochloride*

A solution of 7.5 grams of 5 - benzyloxy-3 - (2 - nitro - 2 - methylethyl) - indole and fifty milliliters of anhydrous ether was added to a solution of ten grams of lithium aluminum hydride and 600 milliliters of ether with stirring and ice-bath cooling. The resulting suspension was refluxed for two and one-half hours and allowed to stand for ten hours at 25 degrees centigrade. The mixture was then cooled in ice and fifty milliliters of water was added, followed by a large excess of fifteen percent aqueous potassium hydroxide solution. The water layer was separated from the ether layer and was extracted with ether. The ether extract was combined with the ether layer and the mixture was washed with water, dried over anhydrous sodium sulphate, and evaporated to about 100 milliliters. Eight milliliters of saturated ethereal hydrogen chloride was then added while swirling in the cold. The resulting precipitate was filtered, washed with ether, and recrystallized by dissolving in 110 milliliters of warm methanol and adding 420 milliliters of ether. The mixture was

to stand for ten hours in the cold, filtered, and washed with ether to yield 4.58 grams of 5-benzyloxy - 3 - (2 - amino - 2 - methylethyl)-indole hydrochloride which melted at 253 to 254 degrees centigrade.

Anal.: Calcd. for $C_{13}H_{21}ClN_2O$: C, 68.23; H, 6.68; N, 8.84; Cl, 11.19
Found: C, 68.39 H, 6.65; N, 8.66; Cl, 10.95.

F. *5 - hydroxy - 3 - (2 - amino - 2 - methylethyl) - indole creatinine sulphate*

Two-tenths of a gram of 5 - benzyloxy - 3-(2 - amino - 2 - methylethyl) - indole hydrochloride was suspended in ten milliliters of water, three milliliters of ten percent aqueous potassium hydroxide solution was added and the resulting oil was extracted twice with ether. The ethereal extract was washed twice with water, once with saturated aqueous sodium chloride solution, and then dried over anhydrous sodium sulphate and evaporated to dryness. A yellow amorphous material (0.128 gram) was obtained. The amorphous material was dissolved in ten milliliters of ethanol and the solution was shaken for two hours at atmospheric pressure in the presence of hydrogen and 0.1 gram of ten percent palladium-on-carbon catalyst. The mixture was filtered and evaporated to dryness. The residue was then dissolved in 0.7 milliliter of 1 N sulphuric acid and two milliliters of water. The resulting solution was filtered to remove a small amount of solid material (one milliliter of water was used to wash), and 86.5 milligrams of creatinine sulphate was added. The solution was frozen and the solvent was removed from the frozen mass under high vacuum. The product, 5 - hydroxy - 3 - (2 - amino - 2 - methylethyl) - indole creatinine sulphate, was thus obtained as a light tan solid. The ultraviolet and infrared spectra were in conformance with the structure of 5 - hydroxy - 3 - (2-amino - 2 - methylethyl) - indole creatinine sulphate.

Anal.: Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64
Found: C, 70.46; H, 5.98; N, 8.80.

B. *5 - hydroxy - 3 - (2 - amino - 2,2-dimethylethyl) - indole*

A solution of 5.0 grams of 5 - benzyloxy-3 - (2 - nitro - 2,2 - dimethylethyl) - indole, 200 milliliters of absolute methanol, approximately 1.0 gram of ten percent palladium-on-charcoal catalyst was shaken for twenty hours under fifty pounds initial hydrogen pressure. When four mole equivalents of hydrogen were absorbed the mixture was filtered through Celite (Registered Trade Mark) and the filtrate was concentrated to dryness under reduced pressure. The solid, 5 - hydroxy - 3 - (2-amino - 2,2 - dimethylethyl) - indole, melted at 74 to 84 degrees centigrade, resolidified, and decomposed upon further heating.

Anal.: Calcd. for $C_{12}H_{16}N_2O.1/2CH_3OH$: C, 68.15; H, 8.23; N, 12.71
Found: C, 68.47; H, 7.95; N, 12.79.

In the same manner as shown in Example 1, Part F, 5 - hydroxy - 3 - (2 - amino - 2,2-dimethylethyl) - indole creatinine sulfate was prepared by using 5 - hydroxy - 3 - (2-amino - 2,2 - dimethylethyl) - indole in lieu of 5 - hydroxy - 3 - (2 - amino - 2 - methylethyl)-indole.

EXAMPLE 2

Preparation of 5 - hydroxy - 3 - (2 - amino-2,2 - dimethylethyl) - indole creatinine sulphate

A. *5 - benzyloxy - 3 - (2 - nitro - 2,2-dimethylethyl) - indole*

Twenty grams of 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole, 100 milliliters of 2 - nitropropane and 5.2 grams of solid sodium hydroxide was agitated by a slow stream of nitrogen and refluxed for approximately eight hours until the evolution of dimethylamine ceased. The reaction mixture was cooled and fifty milliliters of ten percent aqueous acetic acid solution was added. The mixture became warm and the solid dissolved. A 200-milliliter quantity of ether was added and the layers were separated. The ether layer was washed four times with water. A mixture of anhydrous magnesium sulphate, Darco 60 (Registered Trade Mark) (activated carbon) and a filter aid was added, and the mixture was filtered. The solvent was removed under reduced pressure and the residue crystallized upon trituration with ether. The crude crystalline product was recrystallized from benzene to yield 16.4 grams of 5 - benzyloxy - 3 - (2-nitro - 2,2 - dimethylethyl) - indole which melted at 114 to 115 degrees centigrade. After recrystallization from ethanol the compound melted at 114.5 to 116.5 degrees centigrade.

EXAMPLE 3

Preparation of 5 - hydroxy - 3 - (2 - amino-2,2 - diethylethyl) - indole creatinine sulphate

In the same manner as shown in Example 2, 5 - methoxy - 3 - (2 - nitro - 2,2 - diethylethyl) - indole was prepared by utilizing 5-

methoxy - 3 - (dimethylaminomethyl) - indole (Bell et al., J. Org. Chem. 13, 547, 1948), and 3 - nitropentane in place of 5 - benzyloxy-3 - (dimethylaminomethyl) - indole and 2-nitropropane. The resulting 5 - methoxy - 3-(2 - nitro - 2,2 - diethylethyl) - indole was reduced with lithium aluminum hydride and the reduced product was reacted with gaseous hydrogen chloride to produce 5 - methoxy-3 - (2 - amino - 2,2 - diethylethyl) - indole hydrochloride.

The resulting 5 - methoxy - 3 - (2 - amino-2,2 - diethylethyl) - indole hydrochloride was reacted with potassium hydroxide to prepare the free base. The free base was dealkylated with aluminum chloride utilizing the procedure of Asero et al., supra, to produce 5 - hydroxy-3 - (2 - amino - 2,2 - diethylethyl) - indole and the free base was reacted with sulphuric acid and creatinine sulphate to produce 5-hydroxy - 3 - (2 - amino - 2,2 - diethylethyl)-indole creatinine sulphate.

Example 4

Preparation of 5 - hydroxy - 3 - (2 - amino-2,2, - dipropylethyl) - indole hydrochloride

5 - (para - methylbenzyloxy) - indole was prepared using the procedure of Burton et al., supra, and 5 - (para - methyl - benzyloxy)-3 - dimethylaminomethyl) - indole was prepared in the manner disclosed in Example 1, by using 5 - (para - methyl - benzyloxy) - indole in lieu of 5 - benzyloxyindole.

In the same manner as disclosed in Example 2, 5 - (para - methylbenzyloxy) - 3 - (2 - nitro-2,2 - dipropylethyl) - indole was prepared by using 5 - (para - methylbenzyloxy) - 3 - (dimethylaminomethyl) - indole and 4 - nitroheptane in place of 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole and 2 - nitropropane. The resulting 5 - (para - methylbenzyloxy - 3 - (2 - nitro - 2,2, - dipropylethyl) - indole was reduced with lithium aluminum hydride to produce 5 - (para-methylbenzyloxy) - 3 - (2 - amino - 2,2 - dipropylethyl) - indole, and the latter was debenzylated with hydrogen and palladium-on-carbon catalyst to produce 5 - hydroxy - 3-(2 - amino - 2,2 - dipropylethyl) - indole. The debenzylated product was reacted in absolute ethanol with hydrogen chloride to produce 5 - hydroxy - 3 - (2 - amino - 2,2-dipropylethyl) - indole hydrochloride.

Example 5

Preparation of 5 - hydroxy - 3 - (2 - amino-2 - butylethyl) - indole creatinine sulphate

In the same manner as shown in Example 1, 5 - ethoxy - 3 - (2 - nitro - 2 - butylethyl)-indole was prepared by utilizing 5 - ethoxy-3 - (dimethylaminomethyl) - indole (J. Chem. Soc. 2462, 1955) and ethyl α - nitro - α - butylacetate instead of 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole and ethyl α-nitro - α - methylacetate. The thus-produced compound was reduced with lithium aluminum hydride to produce 5 - ethoxy - 3 - (2 - amino-2 - butylethyl) - indole and the reduced product was dealkylated with aluminum chloride according to the procedure of Asero et al., supra, and then reacted with creatinine sulphate and sulphuric acid to produce 5-hydroxy - 3 - (2 - amino - 2 - butylethyl)-indole creatinine sulphate.

Example 6

Preparation of 5 - hydroxy - 3 - (2 - amino-2,2 - dibutylethyl) - indole creatinine sulphate

5 - (para - chlorobenzyloxy) - indole was prepared using the procedure of Burton et al., supra, and 5 - (para - chloro - benzyloxy)-3 - (dimethylaminomethyl) - indole was prepared in the manner disclosed in Example 1 by using 5 - (para - chloro - benzyloxy) - indole in lieu of 5 - benzyloxyindole.

In the same manner as disclosed in Example 2, 5 - (para - chlorobenzyloxy) - 3 - (2 - nitro-2,2 - dibutylethyl) - indole was prepared by using 5 - (para - chlorobenzyloxy) - 3 - (dimethylaminomethyl) - indole and 5 - nitrononane in place of 5 - benzyloxy - 3 - dimethylaminomethyl) - indole and 2 - nitropropane.

The resulting 5 - (para - chlorobenzyloxy)-3 - (2 - nitro - 2,2 - dibutylethyl) - indole was reduced with lithium aluminum hydride to produce 5 - (para - chlorobenzyloxy) - 3 - (2 - amino - 2,2 - dibutylethyl) - indole and the latter was debenzylated with hydrogen and palladium - on - carbon catalyst produce 5-hydroxy - 3 - (2 - amino - 2,2 - dibutylethyl)-indole. The debenzylated product was reacted with creatinine sulphate and sulphuric acid to produce 5 - hydroxy - 3 - (2 - amino - 2,2 - dibutylethyl) - indole creatinine sulphate.

Example 7

Preparation of 5 - hydroxy - 3 - (2 - amino-2 - ethylethyl) - indole hydrochloride

5 - propoxyindole was prepared using the procedure of Blaikie et al., supra, and 5-propoxy - 3 - (dimethylaminomethyl) - indole was prepared in the manner disclosed in Example 1 by using 5 - propoxyindole in lieu of 5 - benzyloxyindole.

In the same manner as disclosed in Example 1, 5 - propoxy - 3 - (2 - nitro - 2 - ethylethyl) - indole was prepared by utilizing 5-propoxy - 3 - (dimethylaminomethyl) - indole and ethyl α - nitro - α - ethylacetate instead of 5 - benzyloxy - 3 - (dimethylaminoethyl)-indole and ethyl α - nitro - α - methyl - acetate. The thus-produced compound was reduced with lithium aluminum hydride to produce 5-propoxy - 3 - (2 - amino - 2 -ethylethyl) - indole. The reduced product was dealkylated with aluminum chloride according to the pro-

cedure of Asero et al., supra and then reacted in aqueous medium with hydrogen chloride to produce 5 - hydroxy - 3 - (2 - amino - 2-ethylethyl) - indole hydrochloride.

EXAMPLE 8

Preparation of 5 - hydroxy - 3 - (2 - amino-2 - ethyl - 2 - methylethyl) - indole sulphate

5 - butoxyindole was prepared using the procedure of Blaikie et al., supra, and 5-butoxy - 3 - (dimethylaminomethyl) - indole was prepared in the manner disclosed in Example 1 by using 5 - butoxyindole in lieu of 5 - benzyloxyindole.

In the same manner as disclosed in Example 2, 5 - butoxy - 3 - (2 - nitro - 2 - ethyl - 2-methylethyl) - indole was prepared by using 5 - butoxy - 3 - (dimethylaminomethyl)-indole and 2 - nitrobutane instead of 5 - benzyloxy - 3 - (dimethylaminomethyl)-indole and 2 -nitropropane. The thus-produced compound was reduced with lithium aluminum hydride to produce 5 - butoxy - 3 - (2 - amino - 2 - ethyl - 2 - methylethyl) - indole. The reduced product was dealkylated with aluminum chloride according to the procedure of Asero et al., supra, to produce 5 - hydroxy-3 - (2 - amino - 2 - ethyl - 2- methylethyl)-indole. The dealkylated product was reacted in aqueous medium with sulphuric acid to produce 5 - hydroxy - 3 - (2 - amino - 2 -ethyl-2 - methylethyl) - indole sulphate.

EXAMPLE 9

Preparation of 1 - methyl - 5 - hydroxy - 3-(2 - amino - 2 - methylethyl) - indole creatinine sulphate

A. *1-methyl-5-benzyloxyindole*

1 - methyl - 5 - benzyloxyindole was prepared by reacting 5 - benzyloxyindole with methyl bromide in the presence of sodium ethoxide in the manner disclosed by Baker, supra.

B. *1 - methyl - 5 - benzyloxy - 3 - (dimethylaminomethyl)-indole*

A solution of fifteen milliliters of dioxane and fifteen milliliters of acetic acid was cooled to ten degrees centigrade and 1.2 milliliters of 37 percent aqueous formaldehyde solution was added. The solution was stirred and 3.3 milliliters of 25 per cent dimethylamine was added. The solution was further cooled and a solution of 3.35 grams of 1 - methyl - 5 - benzyloxyindole and fifteen milliliters of dioxane was added over thirty minutes. The solution was allowed to stand for ten hours and then was mixed with 187 milliliters of water and filtered. The filtrate was mixed with a cold solution of 14.0 grams of potassium hydroxide and 150 milliliters of water, and the mixture was cooled and filtered. The precipitate was washed with water and was dried to yield 3.3 grams (eighty percent) of 1 - methyl - 5-benzyloxy - 3 - (dimethylaminomethyl)-indole. A sample was refluxed with activated carbon in alcohol and filtered. The filtrate was diluted with water to precipitate the 1 - methyl - 5-benzyloxy - 3 - (dimethylaminomethyl)-indole which melted between 48 and 50 degrees centigrade.

Anal.: Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51
Found: C, 78.08; H, 7.86; N, 9.69.

C. *1 - methyl - 5 - benzyloxy - 3 - (2-amino - 2 - methylethyl) - indole*

In the same manner as disclosed in Example 1, 1 - methyl - 5 - benzyloxy - 3 - (2 - nitro-2 - methylethyl) - indole was prepared by utilizing propyl α - nitro - α - methylacetate and 1 - methyl - 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole in place of 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole and ethyl α - nitro - α - methylacetate. The resulting 1 - methyl - 5 - benzyloxy 3 - (2 - nitro-2 - methylethyl) - indole was reduced with lithium aluminum hydride to produce 1-methyl - 5 - benzyloxy - 3 - (2 - amino - 2-methylethyl) - indole which melted between 62 and 64 degrees centigrade.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51
Found: C, 77.87; H, 7.29; N, 9.67.

D. *1 - methyl - 5 - hydroxy - 3 - (2-amino - 2 - methylethyl) - indole creatinine sulphate*

A mixture of 1.0 gram of 1 - methyl - 5-benzyloxy - 3 - (2 - amino - 2 -methylethyl)-indole, 150 milliliters of absolute methanol, and approximately 300 milligrams of ten percent palladium-on-carbon catalyst was subjected to hydrogen pressure at fifty pounds for eight hours. The mixture was treated with 3.5 milliliters of one normal sulphuric acid and filtered. The filtrate was concentrated to dryness under reduced pressure at 40—50 degrees centigrade. The dark residue was dissolved in 16.4 milliliters of water, treated with a trace of activated carbon and filtered. The flask and solids were washed with five milliliters of water. A 500-milligram quantity of creatinine sulphate was added to the combined filtrates. The filtrate was heated to about fifty

degrees centigrade and 105 milliliters of boiling acetone was added. After refrigeration 100 milligrams of creatinine sulphate was precipitated. The mixture was filtered and the filtrate was further diluted with acetone. After two days at five degrees centigrade, 500 milligrams (35 percent) of product, 1 - methyl - 5-hydroxy - 3 - (2 - amino - 2 - methylethyl)-indole creatinine sulphate was collected which was 91 percent pure by ultraviolet assay.

EXAMPLE 10

1-ethyl-5-hydroxy-3-(2-amino-2,2-diethylethyl)-indole acetate

1 - ethyl - 5 - benzyloxyindole was prepared by reacting 5 - benzyloxyindole with ethyl bromide in the presence of sodium ethoxide in the manner disclosed by Baker, supra.

In the same manner as disclosed in Example 1, 1 - ethyl - 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole was prepared using 1-ethyl - 5 - benzyloxyindole in lieu of 5-benzyloxy-indole.

In the same manner as disclosed in Example 2, 1 -ethyl 5 - benzyloxy - 3 - (2 - nitro - 2,2-diethylethyl) - indole was prepared using 1-ethyl - 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole and 3 - nitropentane in lieu of 5 - benzyloxy - 3 - (dimethylaminomethyl)-indole and 2 - nitropropane. The resulting 1-ethyl - 5 - benzyloxy - 3 - (2 - nitro - 2,2-diethylethyl) - indole was reduced with lithium aluminum hydride to produce 1 - ethyl - 5-benzyloxy - 3 - (2 - amino - 2,2 - diethylethyl) - indole and the latter was debenzylated with hydrogen and palladium - on - carbon catalyst to produce 1 - ethyl - 5 - hydroxy - 3 - (2 - amino - 2,2 - diethylethyl)-indole. The debenzylated product was reacted in an ether-absolute ethanol mixture with acetic acid to produce 1 - ethyl - 5 - hydroxy - 3-(2 - amino - 2,2 - diethylethyl) - indole acetate.

EXAMPLE 11

1-butyl-5-hydroxy-3-(2-amino-2-butylethyl)-indole citrate

5 - butoxyindole was prepared using the procedure of Blaikie et al., supra, and 1-butyl-5 - butoxyindole was prepared from 5-butoxyindole and butyl iodide in the presence of sodium ethoxide using the procedure of Baker, supra.

In the same manner as disclosed in Example 1, 1 - butyl 5 - butoxy - 3 - (dimethylaminomethyl) - indole was prepared using 1 - butyl-5 - butoxyindole in lieu of 5 - benzyloxyindole.

In the same manner as disclosed in Example 1, 1 - butyl 5 - butoxy - 3 -(2 - nitro - 2-butylethyl) - indole was prepared using 1-butyl - 5 - butoxy - 3 - (dimethylaminomethyl) - indole and ethyl α - nitro - α - butylacetate in lieu of 5 - benzyloxy - 3 - (dimethylaminomethyl) - indole and ethyl α - nitro - α-methylacetate. The thus-produced compound was reduced with lithium aluminum hydride to produce 1 - butyl - 5 - butoxy - 3 - (2-amino - 2 - butylethyl) - indole. The reduced product was dealkylated with aluminum chloride according to the procedure of Asero et al., supra, and then reacted in absolute ethanol with citric acid to produce 1 - butyl-5 - hydroxy - 3 - (2 - amino - 2 - butylethyl)-indole citrate.

EXAMPLE 12

1 - propyl - 5 - hydroxy - 3 - (2 - amino-2,2 - dipropyl - ethyl) - indole creatinine sulphate

5 - isopropoxyindole was prepared using the procedure of Blaikie et al., supra, and 1-propyl - 5 - isopropoxyindole was prepared from 5 - isopropoxyindole and propyl bromide in the presence of sodium ethoxide, using the procedure of Baker, supra.

In the same manner as disclosed in Example 1, 1 - propyl - 5 - isopropoxy - 3 - (dimethylaminomethyl) -indole was prepared using 1-propyl - 5 - isopropoxyindole in lieu of 5-benzyloxy - indole.

In the same manner as disclosed in Example 2, 1 -propyl - 5 - isopropoxy - 3 - (2 - nitro-2,2 - dipropylethyl) - indole was prepared using 1 - propyl - 5 - isopropoxy - 3 - (dimethylaminomethyl) - indole and 4 - nitroheptane in lieu of 5 - benzyloxy - 3 - (dimethyl - aminomethyl) - indole and 2 - nitropropane. The thus - produced compound was reduced with lithium aluminum hydride to produce 1-propyl - 5 - isopropoxy - 3 - (2 - amino - 2,2-dipropylethyl) - indole. The reduced product was dealkylated with aluminum chloride according to the procedure of Asero et al., supra, and then reacted with creatinine sulphate and sulphuric acid to produce 1 - propyl - 5-hydroxy - 3 - (2 - amino - 2,2 - dipropyl-ethyl) - indole creatinine sulphate.

EXAMPLE 13

1 - butyl - 5 - hydroxy - 3 - (2 - amino - 2-methyl - 2 - propyl - ethyl) - indole creatinine sulphate

5 - benzhydryloxyindole was prepared using the procedure of Burton et al., supra, and 1-butyl - 5 - benzhydryloxyindole was prepared from 5 - benzhydryloxyindole and butyl iodide in the presence of sodium ethoxide, using the procedure of Baker, supra.

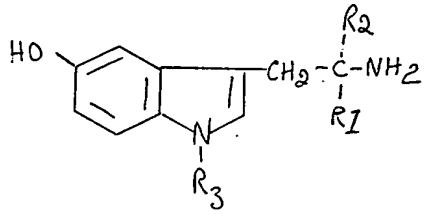
In the same manner as disclosed in Example 1, 1 - butyl - 5 - benzhydryloxy - 3 - (dimethylaminomethyl) - indole was prepared using 1 - butyl - 5 - benzhydryloxyindole in lieu of 5 - benzyloxyindole.

In the same manner as disclosed in Example 2, 1 - butyl - 5 - benzhydryloxy - 3 - (2-nitro - 2 - methyl - 2 - propylethyl) - indole was prepared using 1 - butyl - 5 - benzhydryloxy - 3 - (dimethylamino - methyl)-indole and 4 - nitropentane in lieu of 5-benzyloxy - 3 - (dimethylaminomethyl)-indole

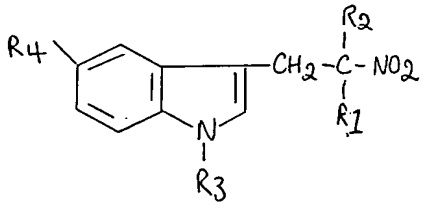
and 2 - nitropropane. The resulting 1 - butyl-5 - benzhydryloxy - 3 - (2 - nitro - 2 - methyl-2 - propylethyl) - indole was reduced with lithium aluminum hydride to produce 1-butyl-5 - benzhydryloxy - 3 - (2 - amino - 2-methyl - 2 - propylethyl) - indole, and the latter was debenzylated with hydrogen and palladium-on-carbon catalyst to produce 1-butyl - 5 - hydroxy - 3 - (2 - amino - 2-methyl - 2 - propylethyl) - indole. The debenzylated product was reacted with creatinine sulphate and sulphuric acid to produce 1-butyl-5 - hydroxy - 3 - (2 - amino - 2 - methyl-2 - propylethyl) - indole creatinine sulphate.

WHAT WE CLAIM IS:—

1. A process for the preparation of a 5-hydroxy - 3 - (2 - amino - 2 -alkylethyl)-indole having the general formula:—



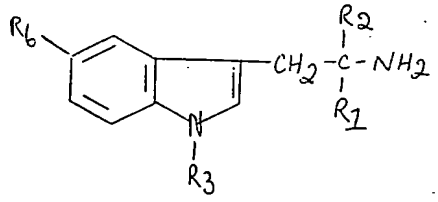
wherein R_2 and R_3 represent hydrogen or an alkyl radical containing from one to four carbon atoms inclusive and R_1 represents an alkyl radical containing from one to four carbon atoms inclusive which comprises the concomitant conversion of a 3 - (2 - nitro-2 - alkylethyl) - indole having the general formula:—



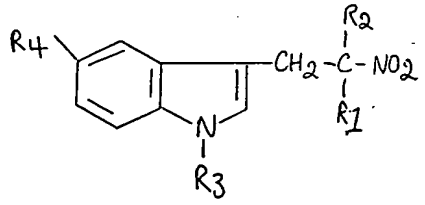
wherein R_4 represents a benzyloxy or benzhydryloxy radical optionally bearing alkyl, alkoxy or halogen substituents and R_2, R_3 and R_1 are as above defined by hydrogenolysis and hydrogenation in the presence of a palladium catalyst to the desired 5 - hydroxy - 3 - (2-amino - 2 - alkylethyl) - indole.

2. A process as claimed in claim 1 wherein the palladium catalyst used is palladium black, palladium-barium sulphate or palladium charcoal.

3. A process for the preparation of a 3-(2 - amino - 2 - alkylethyl) - indole having the general formula:—

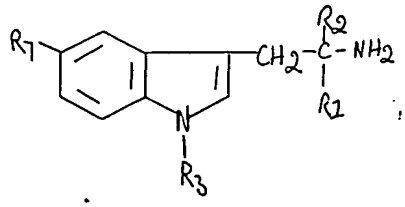


wherein R_6 represents hydroxy or a benzyloxy or benzhydryloxy radical optionally bearing alkyl, alkoxy or halogen substituents, R_2 and R_3 represent hydrogen or an alkyl radical containing from one to four carbon atoms inclusive and R_1 represents an alkyl radical containing from one to four carbon atoms inclusive which comprises subjecting a 3 - (2-nitro - 2 - alkylethyl) - indole having the general formula:—

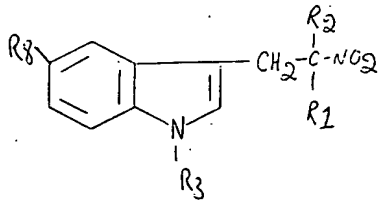


wherein R_4 represents a benzyloxy or benzhydryloxy radical optionally bearing alkyl, alkoxy or halogen substituents and R_2, R_3 and R_1 are as above defined to reduction of the nitro group with lithium aluminium hydride and then if desired to hydrogenolysis of the benzyloxy or benzhydryloxy radical in the presence of a palladium catalyst to produce the desired 5 - hydroxy - 3 - (2 - amino - 2 - alkylethyl) - indole.

4. A process for the preparation of a 3-(2 - amino - 2 - alkylethyl) - indole having the general formula:—



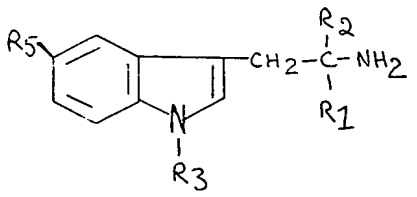
wherein R_7 represents hydroxy or alkoxy, R_2 and R_3 represent hydrogen or an alkyl radical containing from one to four carbon atoms inclusive and R_1 represents an alkyl radical containing from one to four carbon atoms inclusive which comprises converting a 3 - (2-nitro - 2 - alkylethyl) - indole having the general formula:—



wherein R_8 represents an alkoxy radical and R_2, R_3 and R_1 are as above defined by reduction of the nitro group and then if desired dealkylation with aluminium chloride to the desired 5 - hydroxy - 3 - (2 - amino - 2-alkylethyl) - indole.

5. A proces as claimed in claim 4 wherein the reduction is carried out with lithium aluminium hydride or with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum oxide or palladium.

6. A compound having the general formula: —



wherein R_1 represents an alkyl radical containing from one to four carbon atoms inclusive, R_2 and R_3 represent hydrogen or an alkyl radical containing from one to four carbon atoms inclusive and R_5 represents hydroxy, a benzyloxy or benzhydryloxy radical optionally bearing alkyl, alkoxy or halogen substituents and containing up to 15 carbon atoms or an alkoxy radical containing up to 8 carbon atoms provided that R_2 and R_3 do not represent hydrogen simultaneously and acid addition salts thereof.

7. A 5 - hydroxy - 3 - (2 - amino - 2,2-dialkylethyl) - indole.

8. 5 - Hydroxy - 3 - (2 - amino - 2,2-dimethylethyl) - indole creatinine sulphate.

9. 5 - Hydroxy - 3 - (2 - amino - 2,2-dimethylethyl) - indole.

10. 1 - Methyl - 5 - hydroxy - 3 - (2-amino - 2 - methylethyl) - indole creatinine sulphate.

11. 1 - Methyl - 5 - benzyloxy - 3 - (2-amino - 2 - methylethyl) - indole.

12. A process for the preparation of a compound as claimed in any of claims 6 to 11 substantially as herein described with reference to any of the Examples.

13. A compound as claimed in any of claims 6 to 11 when prepared by a process as claimed in any of claims 1 to 5 or 12.

For the Applicants: —
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52 Chancrey Lane, London W.C.2.

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949 to patent Nos. 807,877 and 807,876.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1962.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.